3-19-2018

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HHS Public Access

Author manuscript

J Patient Saf. Author manuscript; available in PMC 2019 September 19.

Hydrophilic Polymer Embolism: Implications for Manufacturing, Regulation, and Postmarket Surveillance of Coated Intravascular Medical Devices

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Abstract

Hydrophilic polymers are ubiquitously applied as surface coatings on catheters and intravascular medical technologies. Recent clinical literature has heightened awareness on the complication of *hydrophilic polymer embolism* (HPE), the phenomenon wherein polymer coating layers separate from catheter and device surfaces, and may be affiliated with a range of unanticipated adverse reactions. Significant system barriers have limited and delayed reporting on this iatrogenic complication, the full effects of which remain under-recognized by healthcare providers and manufacturers of various branded devices. In 2015, the United States Food and Drug Administration acknowledged rising clinical concerns and stated that the agency would work with stakeholders to further evaluate gaps that exist in current national and international device standards for coated intravascular medical technologies. The present article reviews current knowledge on this complication as well as factors that played a role in delaying detection and dissemination of information and new knowledge once hazards and clinical risks were identified. Furthermore, organ-specific effects and adverse reaction patterns are summarized, along with implications for device manufacturing, safety testing, and regulation. Particulate analyses and

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Conflicts of Interest: All authors declare no conflicts of interest

Verification: All authors had access to the data and a role in writing this manuscript

Supplementary Information:

United States Food and Drug Administration Class I Medical Device Recalls (2010-2016)

Meier Steerable Guidewire (Boston Scientific Corporation, Maple Grove, MN); Fathom"-14 Steerable Guidewire (Boston Scientific Corporation, Maple Grove, MN); QuickCat Extraction Catheter (Spectranetics Corporation, Colorado Springs, CO); Synchro 2 Guidewire (Boston Scientific Corporation, Fremont, CA); ZFlex 270 Steerable Sheath (Greatbatch Medical, Minneapolis, MN); MobiCath BiDirectional Guiding Sheath (Greatbatch Medical, Minneapolis, MN); Archer Super Stiff Guidewire (Medtronic Inc., Saint Paul, MN); Angiography Pack (Medline Industries, Waukegan, IL); Cougar Nitinol Workhorse Guidewire (Medtronic Vascular, Danvers, MA); HT Connect Peripheral Guide Wire (Abbott Vascular, Inc, Temecula, CA); Pipeline Embolization Device (Micro Therapeutics Inc, Irvine CA); FindrWIRZ Guidewire System (SentreHeart Inc, Redwood City CA); Alligator Retrieval Device (Micro Therapeutics Inc, Irvine CA); XCelerator Hydrophilic Exchange Guidewire (Micro Therapeutics Inc, Irvine CA); Pipeline Embolization Device (Micro Therapeutics Inc, Irvine CA); and Marathon Flow Directed Micro Catheter (Micro Therapeutics Inc, Irvine CA).

general enhanced processes for device surveillance are needed to optimize vascular technologies and to ensure patient safety.

Keywords

Adverse event; Hydrophilic polymer embolism (HPE); Medical device report (MDR); Particulate safety limits; Postmarket surveillance; Regulation; Vascular device; 510(k) process

Introduction

Hydrophilic polymers are ubiquitously applied as surface coatings on modern intravascular medical technologies. These include guidewires, introducer and delivery sheaths, implantable stents and coils as well as cardiac, central and peripheral catheters. Hydrophilic coatings such as polyvinylpyrrolidone (PVP), polyacrylamide (PAM), polyoxyethylene (PEG), polysaccharides and proprietary co-polymer blends imbibe water and expand when subjected to aqueous environments. These coatings were introduced in the 1980s following recognition of their unique capabilities in increasing lubricity, enhancing hemocompatibility, and enabling targeted intravascular drug delivery while improving drug compliance. With major trends toward minimally invasive techniques and novel drug delivery systems, applications of medical polymer device coatings continue to grow worldwide, with global demands predicted to net $11.8 billion by 2021 [1].

Despite trends and advancements in endovascular techniques and capabilities, significant adverse effects have been linked with coated device use in various postprocedural clinical settings [2-7]. Unanticipated biological reactions including delamination and degradation of device surface materials, with subsequent embolism of released coating particulates within the bloodstream, have increasingly been reported following routine intravascular device use. We first reported fatal complications to the United States Food and Drug Administration (FDA) in 2009 and hypothesized that morbidity and mortality due to iatrogenic *hydrophilic polymer embolism* (HPE) were clinically underrecognized [8,9]. In recent years, additional iatrogenic hydrophobic polymer coating reactions have been described, and accumulating adverse event reports over the past decade provide evidence that clinical complications from device coatings and particulates have not been fully realized.

A review on this topic reveals significant barriers and lags in investigating and reporting on medical HPE complications [10]. Furthermore, there were significant delays in dissemination of knowledge once new hazards and clinical risks were identified [11]. Today, three decades following the introduction of coated vascular medical devices for clinical applications, the full scope of HPE coating complications continues to be understated. Postmarket data on the subject are sparse in the published literature, although available information suggests clearly the need for further investigation and extensive quality improvement initiatives. The present article reviews current knowledge on HPE-related complications and summarizes organ-specific effects, along with implications for device manufacturing, safety testing, and regulation.

Search Parameters and Materials Reviewed

In compiling this review, several sources of relevant literature and information were queried. Pubmed/MEDLINE was searched for reports published from 1986 to 2016, using the terms “hydrophilic polymer embolism”, “HPE” and “polymer coating emboli”. Pertinent citations and references from identified reports were extracted for further evaluation. Manuscripts with available histopathologic data, published in the English language, and unpublished cases and consults in our files with documented HPE were included in the analysis. United States FDA guidelines and communications, postmarket surveillance procedures, available manufacturer literature, medical device recalls and standards for vascular device clearance were additionally evaluated. Outcomes of previous manuscript submissions, including our experience in publishing on this subject over the past decade were assessed. Particulate size dimensions, adverse events, factors that delayed or prevented publication of HPE observations, and a timeline of publication and regulatory activities on the topic are summarized.

Limited Investigation and Subtle Histopathologic Appearances

In the absence of clinical suspicion for iatrogenic coating complications, and without targeted histopathologic analysis, HPE eluded clinical detection for many years (Fig. 1). Recognition of clinical HPE phenomena requires directed biopsy of vital tissues, thorough postmortem analysis of organs and vasculature, and/or evacuation of embolic or thrombus material for definitive histologic detection [3-5]. Declining hospital autopsy rates, lack of reimbursement for postmortem procedures and limited research funding and support in this area are additional factors that hindered documentation and reporting of iatrogenic HPE complications. While histologic analysis remains the only available methodology for definitive diagnosis, subtle microscopic appearances of intravascular polymer and limitations of tissue sampling led to frequent false negative interpretations and significant underreporting [4,5]. The non-polarizable and non-refractile histologic characteristics of this foreign material allowed it to be repeatedly overlooked by experienced pathologists as incidental findings or artifacts of tissue processing and staining. Fluctuating *in vivo* histologic appearances resulting from associated intravascular hydration, degradation and inflammation further shrouded diagnosis of many cases (40). Lack of available corroborative methodologies for determination of embolic degree also complicated extent of reporting. Furthermore, variable experience among diagnostic physicians precluded consensus guidelines for reporting. With expanded knowledge and gradual increase in recognition of predicted tissue appearances and effects, however, there has been a marked increase in HPE reporting over recent years (Fig. 1, Table 1) [2-44].

Reported Adverse Events, Contributory Devices and Incidence

Following localized access site deposition or embolism to distal organs, polymeric deposits measuring up to 1.9 mm in cross section and 2.3 cm in longitudinal section, have been shown to induce vasoocclusion, in most cases with associated intra- and/or peri-vascular inflammation, thrombus formation, and/or fibrosis (Fig 2, Table 2). Adverse reactions have been documented in patients aged 2 months to 89 years [43,44] and have involved the heart [5,19-21,24,27,29,33], lungs [4,5,10,28], brain [2,3,5,8,9,18,22,30,40,43], kidneys [21,23],

skin/subcutaneous tissues and extremities [12-17,25,26,31,32,44], arteriovenous and transplant grafts [9,21], colon [35], spinal cord [5], liver [7], spleen, pancreas, adrenal glands and muscle (Table 1), and on occasion have been associated with multisystem involvement, including multiple organ failure and/or systemic inflammatory response syndrome [5,7]. Recognized organ-specific reactions and clinical sequelae are summarized in Table 2. While reactions are often incidental or of unclear clinical significance, significant secondary reactions have been found to recur or persist in some patients for several years [7]. Factors impacting on clinical outcomes have been shown to include embolic number, embolic size(s), embolic morphologies, afflicted organ(s), site(s) of tissue or organ involvement, co-existing patient morbidities and severity of secondary tissue reactions [5,7,40]. Symptomatic responses may be self-limiting, or alternatively, may lead to focal or multifocal parenchymal necrosis with potential disability due to symptomatic vital organ or limb infarction and/or patient death (Table 2). Due to multiplicity of clinical procedures and instruments used, causative devices have often been indiscernible on retrospective exams, despite the fact that a wide variety of procedures and device types were recognized to be contributory [5,9]. While hospital autopsy analyses have revealed postmortem HPE frequencies of 10-13% [5,33], clinical evidence from targeted *in vivo* investigations highlight incidences of up to 45-86% in select populations [33,36,39].

Barriers to Investigating, Publishing and Reporting

Submitted manuscripts on this subject underwent rigorous review at multiple journals, with up to six reviewers per journal and mean total review time of 2 years per single manuscript [5,6,8-10]. Contradictory reviewer comments resulted in multiple rejections, and often included concerns that reports were not of clinical significance and that associated findings would have little or no impact on device manufacturing, user guidelines or regulation [11]. The majority opinion among cardiovascular interventional reviewers was that postmortem interpretations were of limited clinical relevance and that HPE were epiphenomena of intravascular device use. Additional editorial comments included statements that the subject matter was low priority for publication or was outside the desired scope of various clinical and subspecialty journals. Competing interests resulted in manufacturer hesitancy to disclose proprietary coating compositions and manufacturing processes, avoidance of reporting by treating physicians, mitigation of institutional reporting and liability by administrators and risk management; and limitations on resources and support for detailed diagnostic investigation and formal quality improvement initiatives. Other factors that hindered or precluded reporting included high physician clinical workloads; absence of standardized hospital adverse event reporting system(s); unclear procedure(s) and limited receptivity for near miss reporting; voluntary and open-ended nature of federal adverse event reporting forms; lack of interdisciplinary communication; lack of institutional cooperation in patient and device reporting; absence of available preclearance or postmarket data and device information for corroboration of new findings; absence of feedback and transparency during formal reporting processes; lack of clarity and awareness regarding which physician or system member should report; general lack of support and network for young female and minority investigators; and editorial rejection of additional case encounters due to stated lack of “novel findings”. Factors impacting on HPE investigation, publication and reporting are summarized in Fig 3.

Regulatory Activities, Device Discontinuations and Device Recalls

Despite compounding challenges associated with HPE reporting, documentation of adverse events continues to influence global trends in vascular device manufacturing, regulation and clinical practices (Fig. 1). Following initial case descriptions by Barnwell et al. in 1997, the Fastracker-18 microcatheter was discontinued by the manufacturer (Target Therapeutics, Fremont, Calif) [2]. Following recognition of localized access site complications by Kozak et al. in 2003, warning labels were instituted on specific branded vascular sheaths (Cook Inc., Bloomington, IN) [13]. Following reports of morbidity and mortality associated with distal embolism from multiple device types in 2008-2010 [3,4,8,9], FDA guidance recommendations were put forth for industry and regulatory staff regarding particulate testing of stents, delivery systems and percutaneous transluminal coronary angioplasty (PTCA) catheters [41]. In 2010, International Standard ISO 10993-13 was revised, providing general requirements for preclinical simulated use testing of polymeric medical devices [42]. An FDA communication entitled “Critical to Quality (CtQ) Indicators: Hydrophilic Coated and Hydrophobic Coated Vascular and Neurological Devices” was drafted to manufacturers in 2015, summarizing coated device features that may be pertinent to device safety [45]. Following publication of postmortem HPE frequencies in 2015 [5,33], the FDA increased surveillance by retrospectively reviewing medical literature, medical device reports (MDRs), device labeling and recalls, and by actively soliciting information from physicians, engineers and manufacturers [7,46,47]. FDA investigation revealed almost 500 MDRs, 9 mortalities and multiple device recalls due to HPE. An FDA Safety Communication entitled “Lubricious coating separation from intravascular medical devices” was issued in November, 2015, alerting treating and diagnostic physicians on potential hazards and risks of polymer coatings and providing recommendations for safe clinical practices [46]. In all, 16 coated intravascular medical devices were recalled by the FDA between 2010 and 2016, due to separation of lubricious coating materials. These included various branded guidewires, sheaths, retrieval devices and embolization device delivery wires (see Supplementary Information, Class 1 Medical Device Recalls).

Clearance Standards for Coated Intravascular Medical Technologies

To date, premarket evaluation requirements for coated vascular medical devices incorporate studies of coating durability and friction, with recommendations put forth for inspection of integrity of device surface coatings. While regulatory attention to intravascular device coating quality and integrity has heightened over recent years, device-specific clinical performance and safety data remain unavailable to hospitals, device users and patients who consent and undergo intravascular medical procedures. Furthermore, current standards do not strictly define allowable size thresholds, nor overall permissible limits for particulates generated during *in vitro* testing of coated vascular medical technologies. Section 6 of the AAMI TIR 42 states “because of the absence of comprehensive and definitive clinical data, particle size ranges and particle count limits are not recommended in this TIR” [41]. The International Organization for Standardization 10993 Standard Series (ISO10993), entitled “Biological evaluation of medical devices”, puts forth guidelines for preclearance evaluation of hydrophilic vascular medical device biocompatibility and safety, incorporating requirements for preclinical testing of device-induced cytotoxicities, immunotoxicities, hemocompatibility, and polymeric degradation, among other factors [42]. Part 13 of the

Standard, entitled “Identification and quantification of degradation products from polymeric medical devices”, provides general requirements for evaluating particulates released from polymeric medical device surfaces, when subjected to simulated clinical environments. Notably, recommended studies are performed by individual manufacturers via nonstandardized protocols [41]. Applicants most often provide FDA with evidence that new devices are “substantially equivalent” to devices already on the market (i.e., predicate devices). Devices can then be cleared by 510(k) processes, which do not require any clinical testing prior to formal product release. Thus, analyses of the distal vasculature, organ-associated responses and/or long-term biological polymer effects in living systems are not specifically evaluated, and to date their effects remain unknown. Furthermore, standardized methodologies for *in vivo* device testing are currently unspecified [42].

Need for Additional Premarket and Postmarket Oversight and Device Monitoring

While recommendations outlined in AAMI TIR 42 [41] suggest that manufacturers introducing new devices should obtain comparative data on particulate matter from predicate devices, the safety and efficacy of predicate devices are unproven. Furthermore, clinical evidence shows that established pre-clinical simulated use testing is not fully predictive of device coating performances in real-world settings [2-46]. Current ISO10993 standards do not specify *in vivo* testing procedures for degradable polymeric devices, including screening of device surface changes upon animal or human blood contact, analyses of vessel-device interface reactions, determination of degree, quality and/or rates of intravascular coating biodegradation and particulate release, or analyses of biological implications of polymer deposits within distal vasculature and end-organs [5,6,42]. Additional experimental and clinical testing and device analyses are therefore needed. Coordinated efforts in this area would allow for more accurate, comprehensive and integrated device evaluation and surveillance, while promoting more timely, reliable and direct feedback regarding patient risks and device performances to patients, physicians, manufacturers, additional industry personnel and the FDA (Fig. 4).

Etiologies for Polymer Abrasion - Mechanical Factors and Need for Additional *In Vitro* Device Testing

Mechanical factors that may influence polymer coating delamination from vascular device surfaces include excess friction, such as with coated device use in tortuous, atherosclerotic, narrowed and/or attenuated vessels [40,43]. Passage of devices across acutely angulated bifurcation sites, manipulation of tight-fitting device combinations, coaxial techniques involving curved, irregular, stiff or sharp edged devices, and multiple difficult attempts at vascular cannulation [40,45] likely further contribute to surface disruption. Operator skill, specific device types, coating compositions, intrinsic base coat bonding properties, curing processes, and device coverage styles such as complete versus partial device coverage, submicron (thin) versus micron (thick) coats and device surface substrate modification have additionally been shown to influence incidences of mechanical polymer peeling and flaking from device surfaces [7,33,48,49]. Frequency of intravascular procedures and devices used, improper handling or use of devices including incorrect sizing or reshaping, and use of damaged or expired devices likely additionally predispose to mechanical disruption and coating abrasion. Expanded, systematic *in vitro* device testing is therefore needed to assess

contributory chemical, manufacturing, storage, operator and patient-related factors that predispose to mechanical coating disruption and delamination.

Etiologies for Polymer Biodegradation – Hydration and Biological Factors and Need for Additional *In Vivo* and *Ex Vivo* Device Testing

Surface biomaterials may be further compromised due to dissolution in solutions and/or air. Degradation during product development, storage and use would be expected to vary with polymer bonding and composition(s), and in many cases would be critically time-dependent. Variable rates of bond breakage would be expected to occur upon subjection of devices to different aqueous and/or biological conditions [6,10,40]. Evaluation of device surface qualities and degradative time courses along various stages of product lifecycle is therefore warranted to allow for better understanding of safety, coating integrity, and particulate release. Coating degradation may result from improper or suboptimal device processing (e.g., heat versus ultraviolet curing or light exposure), packaging and storage (e.g., sustained or suboptimal temperatures or humidity), sterilization method (e.g., autoclaving, irradiatiation or use of ethylene oxide), and preparation (e.g., prolonged hydration and/or use of incorrect solutions). Moreover, rapid biodegradation may be associated with prolonged blood contact, extended procedural times, and baseline patient conditions. In light of diverse clinical scenarios and complexities of device manufacturing, storage, preparation and use, investigation of device-specific biodegradation and vascular reaction patterns under controlled clinical environments, incorporating real-world conditions in distinct patient subsets, and under different environmental conditions of manufacturing, sterilization, storage, and use would be highly relevant [5,6,42,50]. Expanded *in vivo* and *ex vivo* device testing for investigation of surface integrity and measures of particulate release is needed to provide safety data regarding individual device use and potential for long-term biological effects [6,7,10].

Unique Considerations of HPE in Distinct Patient Subsets

Risks associated with HPE phenomena likely further vary in distinct patients, due to unique anatomical and clinical considerations. As friction resulting from device–vessel and device–device contact may be a primary etiological factor predisposing to surface shearing, attenuated vessel caliber and incorrect device sizing may introduce distinct risks within the infant, pediatric, adolescent, and adult female and male populations. Structural cardiac abnormalities and presence of right-to-left cardiac shunts would predispose to cerebrovascular and systemic embolic events. Immature infant and pediatric organs would be more susceptible to multifocal foreign body deposition and inflammatory and developmental sequelae. Cumulative subclinical responses would likely result in additive complications over the course of a lifetime in patients who are younger and undergo repeated endovascular procedures or harbor chronic indwelling catheters or implanted devices. Furthermore, embolic events are more likely to be symptomatic among patients with compromised baseline vascular reserve or comorbid disease including acidosis, immunosuppression, hyperinflammation, or potential toxicological or pharmacological interactions. Given potential diverse clinical effects, optimal coating applications and thicknesses may be investigated in patient subsets to determine permissible thresholds in distinct organ systems and populations treated. In particular, safety standards may be more

stringently imposed with regard to pediatric devices, due to potential for long term effects and unique size considerations with propensity for vasoocclusion in distal small vessels and developing organs.

Overall Implications for Manufacturing, Regulation and Device Surveillance

A review on HPE raises several red flags and highlights inefficiencies in multiple systems, both within the United States and internationally. The HPE issue was overlooked and perpetuated due to cumulative flaws and gaps in existing systems for medical peer-review, medical device clearance, medical device surveillance and facility auditing (Fig 3). An exhaustive 2011 Institute of Medicine (IOM) analysis, conducted at the request of the FDA, concluded that the 510(k) process for medical device clearance is intrinsically flawed and suggested that the device approval system in the United States should be replaced [51]. The current review illustrates specific failures of the 510(k) process as well as MDR-based postmarket surveillance processes in regard to identifying and addressing critical adverse device events and emerging trends [52].

Notably, since physicians are not specifically required to investigate or report adverse device events, underreporting persists as a major impediment of current voluntary reporting systems. Although facilities are required to report detected adverse events, no specific penalties are imposed for not reporting. Inefficiencies of voluntary facility reporting systems were documented in a 2010 Office of Inspector General (OIG) Report which found that incident reports were not generated for 93% of events in hospitals surveyed [53]. Moreover, as stated in a 2016 Duke-Margolis Center for Health Policy Report, weakness in the current postmarket surveillance system “significantly affects public health and biomedical innovation, by creating obstacles for patients and clinicians to receive the meaningful information they need to make informed decisions, perpetuating unnecessarily long delays and gaps in effective and timely safety communications and recall management, hindering the timely development of new and innovative treatment options, and increasing the overall costs and inefficiency of the health care system.” [54].

The 2015 FDA Safety Communication on lubricious device coatings acknowledged rising concerns and gaps in national and international standards for coated vascular devices and stated that the agency would work with stakeholders to develop nonclinical test methodologies and establish device performance criteria to address these gaps [46]. In 2016, the FDA awarded the Medical Device Innovation Consortium (MDIC), a 501(c)(3) public-private partnership created for the purpose of advancing pre- and post-market investigations into safety of medical devices, with $3 million in seed funding to establish a Coordinating Center for the National Evaluation System for health technology (NESTcc). Stated organizational goals of NESTcc include introducing patient-centered approaches to medical device surveillance, increasing cost-effective use of real-world evidence (RWE) across total product lifecycles (TPLC), promoting projects to facilitate evidence generation and data sharing, and engaging various stakeholders across medical device ecosystems through outreach and educational activities. To date, however, a concrete plan for corrective action to the HPE issue has not materialized.

Next Steps and Need for Device Registries for Further Clinical HPE Characterization

Assurances of medical device safety are a collective responsibility and benefit all system members – patients, healthcare payers and providers, manufacturers, and the FDA. Each party has a distinct role in promoting the wellbeing of patients, and without interdisciplinary discussion and sharing of information, progress on medical device safety issues cannot occur [55-58]. The assembly of consortia amenable to more open communication and more proactive and innovative investigative approaches for device performance and safety testing is needed. To more efficiently assess product designs, histopathological HPE evidence and epidemiological data, development of standardized testing methods for vascular devices would be required, along with formal partnerships between regulators, manufacturers, and treating and diagnostic physicians. Formal, large-scale device databases and centralized tissue registries should be developed to allow for systematic reporting and facilitate investigation of device events. While the need for an infrastructure for institution of national device-specific registries has been acknowledged by the FDA [59], it remains unclear how this would be implemented in regard to investigation of coated vascular medical technologies, who would be responsible for supporting and funding these initiatives, and how non-biased physicians and researchers with interdisciplinary expertise and knowledge would be incorporated into an appropriate system of oversight.

The current manuscript summarizes histopathological evidence regarding *in vivo* HPE reactions that could be further analyzed and incorporated as end-points for systematic postmarket device surveillance. Available information regarding diagnostic imaging and laboratory findings have been summarized [5,6,40]. Continued and expanded work on this subject should include determination of optimal methods to quantitate polymer particulate release, both *in vitro* and *in vivo*, and to systematically evaluate secondary HPE reactions in living systems. Standardized testing would help bring public safety information regarding device-specific and coating-specific performances [6,49,60]. A universal, sensitive and specific testing method for measuring coating particulates from vascular medical devices, however, will not be feasible. Rather, a battery of relevant screening and testing methods would be needed to accurately capture qualities and rates of particulates generated under various environmental and biological conditions, and at various stages of product lifecycles. Given the complexity and diversity of intravascular device types, available coating compositions, applications and curing processes, etiologies for delamination, clinicopathological HPE effects, and underlying patient comorbidities, large-scale investigations are needed to allow for more meaningful and comprehensive analyses. Until causes and effects of coating particulates are better understood, and until definitive standards can be determined, research in humans and experimental models would be beneficial to increase knowledge on appropriate testing methods and considerations for patient safety.

Priority areas for future investigation should include further characterization of intermediate- and long-term biological responses of distinct polymeric agents within the human bloodstream, elucidation of temporally heterogeneous organ-specific iatrogenic effects, and determination of time-dependent coating degradation as pertains to usage and distinct device designs. Likewise, understanding and stratifying the clinical effects of various particulate compositions, and effects of particulate sizes and burdens in distinct organs and vascular

territories will be required to establish acceptable thresholds and permissible polymer particulate limits. New standards would likely be distinct for different coating types (e.g., synthetic versus natural materials), vascular territories instrumented (e.g., intracerebral versus intracardiac, peripheral vascular, or other site), intended use and duration (e.g., 1 hour versus 1 day, 1 month, or beyond), and population treated. Elucidation of the role of patient age, gender, comorbidities and concomitant pharmacotherapies in pathogenesis, metabolism and excretion of HPE, would be critical for bringing increased knowledge to help optimize device technologies and facilitate better device selections for future patients [6,46,60].

Conclusions

While lubricious polymers have distinct advantages for application as vascular medical device coatings, detection of adverse clinical events attributed to their use have steadily increased over the past decade, coinciding with increasing coated device use and complexities of endovascular procedures and technologies. Moreover, HPE effects have proven to be complex and highly variable, depending on particulate sizes and load, coating and device compositions and designs, temporal related factors and various patient comorbidities. These complexities suggest a need for updated approaches to testing and monitoring clinical benefits and risks of existing and new devices. Increased attention to device-specific polymer particulate release and coating performances should be a priority area for future medical research, manufacturing and regulation. Given the nature of biomaterial coatings and potential risks, safety testing for newly introduced coated intravascular medical device types should incorporate systematic tissue-based and/or clinical monitoring to allow for risk assessment in real-world settings. Novel materials, device surface substrate modifications, and/or alternative coating methodologies should be investigated to further optimize safety and efficacy of future devices.

In regard to general device safety testing and investigation, the FDA has cited a lack of financial support for programmatic change. Analyses of the postmarket surveillance system by the Brookings Institution stated that increased congressional support, FDA engagement and appropriations are needed to create and sustain the appropriate infrastructure and public-private partnerships necessary for a robust and effective medical device surveillance system in the United States [54]. Our experience and independent analyses reveal that lack of incentivization and dedicated support for physician investigators is a primary hindrance to timely investigation and progress in the field. Thus, comprehensive work on this subject would depend on development of an appropriate infrastructure and identification of funding sources for collaborative investigation on vascular medical device coatings and associated risks. Despite challenges in this area, the significant global public health relevance warrants increased attention to enhance patient safety and help bring critical system and device improvements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

R.I.M. (Rupal I. Mehta) is supported by a grant from the National Institute of Neurological Disorders and Stroke (K08NS089830).

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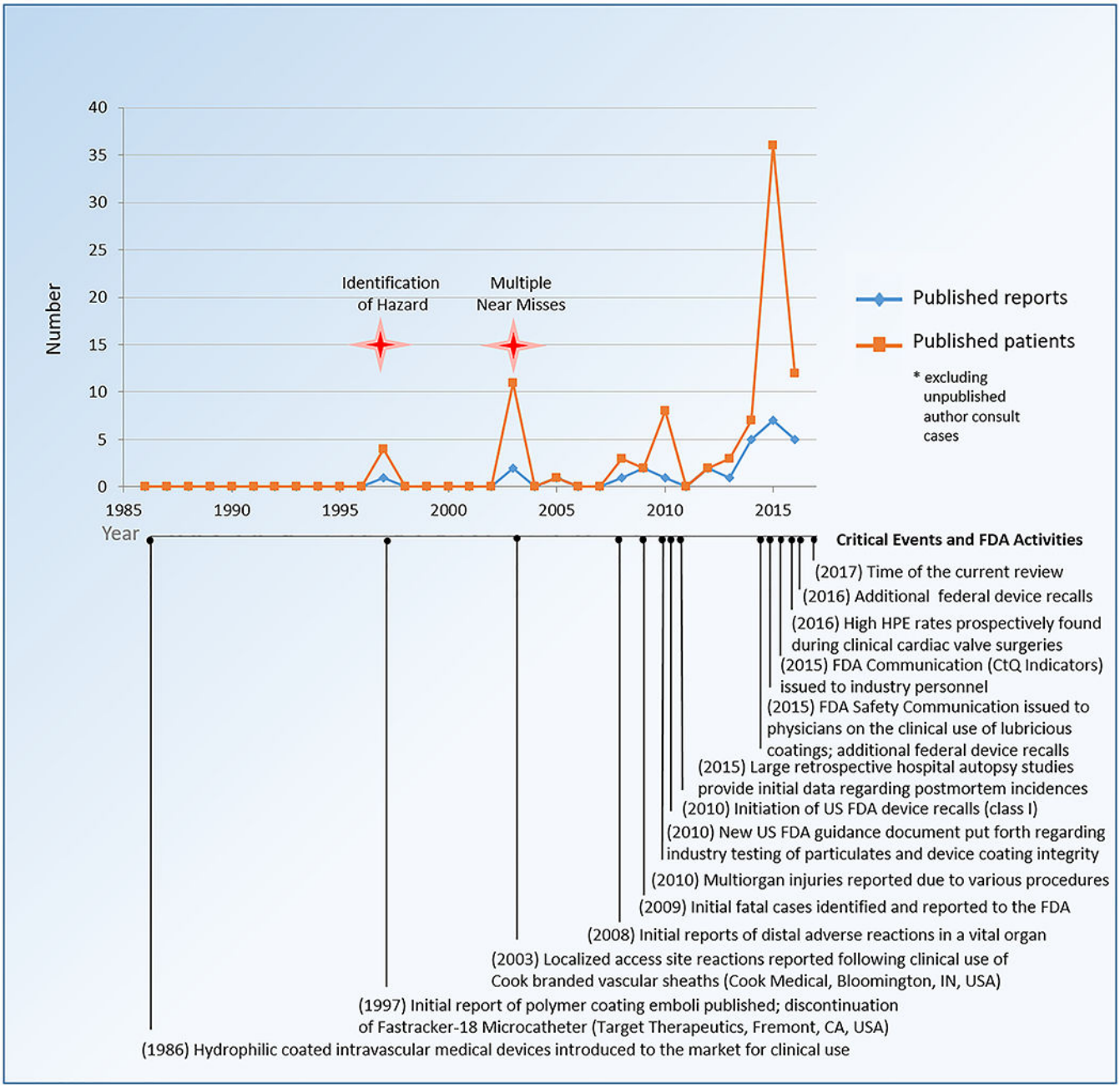

Figure 1. Timeline and Evolution of Coated Intravascular Medical Device Technologies

The published clinical literature (1986-2016), highlights a gradual increase in HPE reporting over the course of three decades, with increasing recognition of implications for public health and safety.

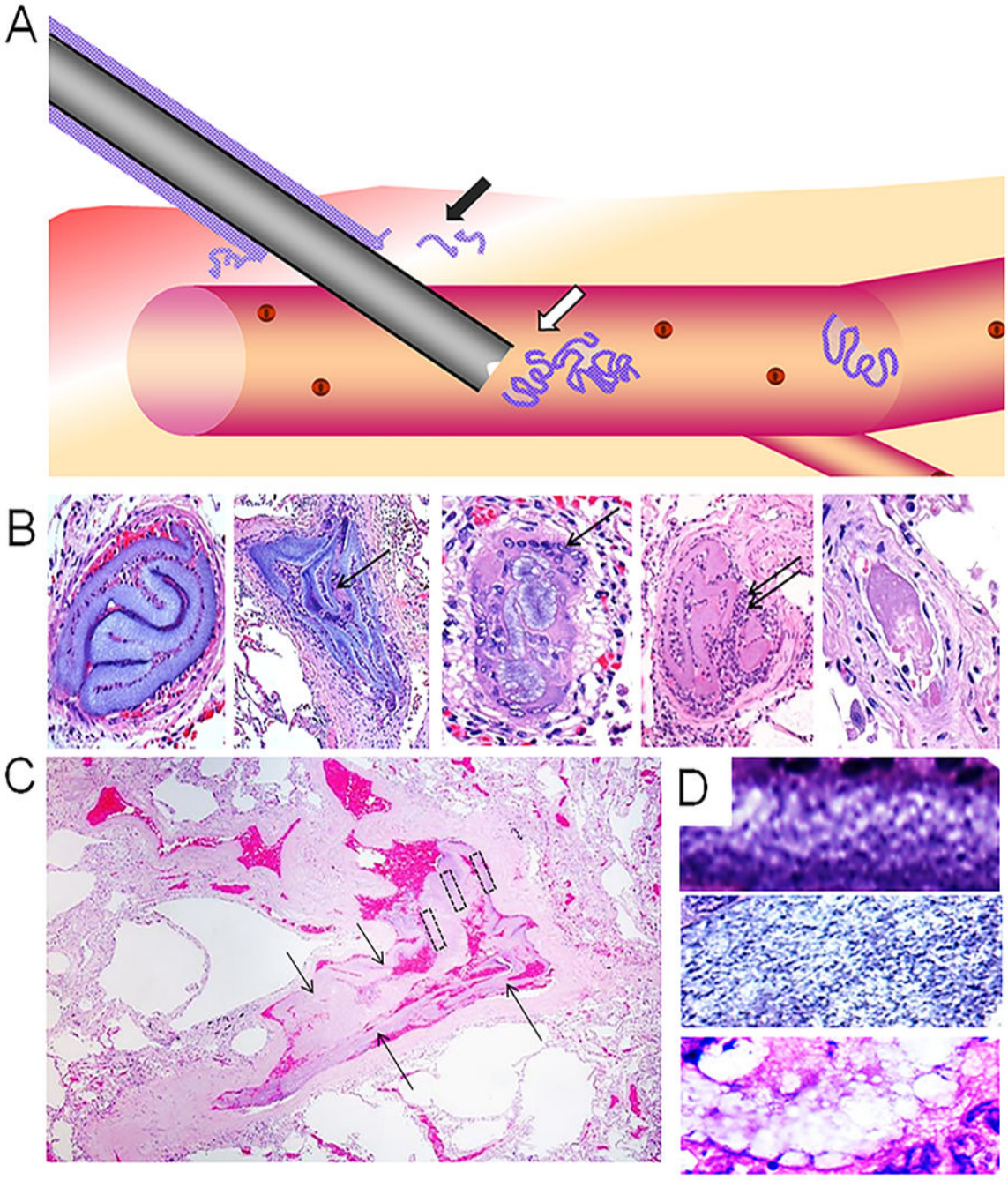

Figure 2. HPE Formation and Heterogeneous Histologic Appearances

(A) Depiction of polymer delamination from a vascular medical device surface, with localized access site deposition (black arrow) and embolic phenomena (white arrow); **(B)** Histologic features include basophilic, granular, coiled intravascular foreign bodies, with associated giant cells and granulomata (single arrow) and/or neutrophilic response (double arrows); gradual intravascular degradation may result in progressive eosinophilic change (i.e., pink coloration), as seen from left to right; **(C)** Low-power scanning microscopy may reveal heterogeneous degradation of HPE (arrows), with mimicry of native tissues; **(D)**

High-power images (boxed areas in C) demonstrate variable light microscopic appearances; **(B-D)** Hematoxylin and eosin stain; **(B)** 400X; **(C)** 40X; **(D)** 1000X (oil immersion).

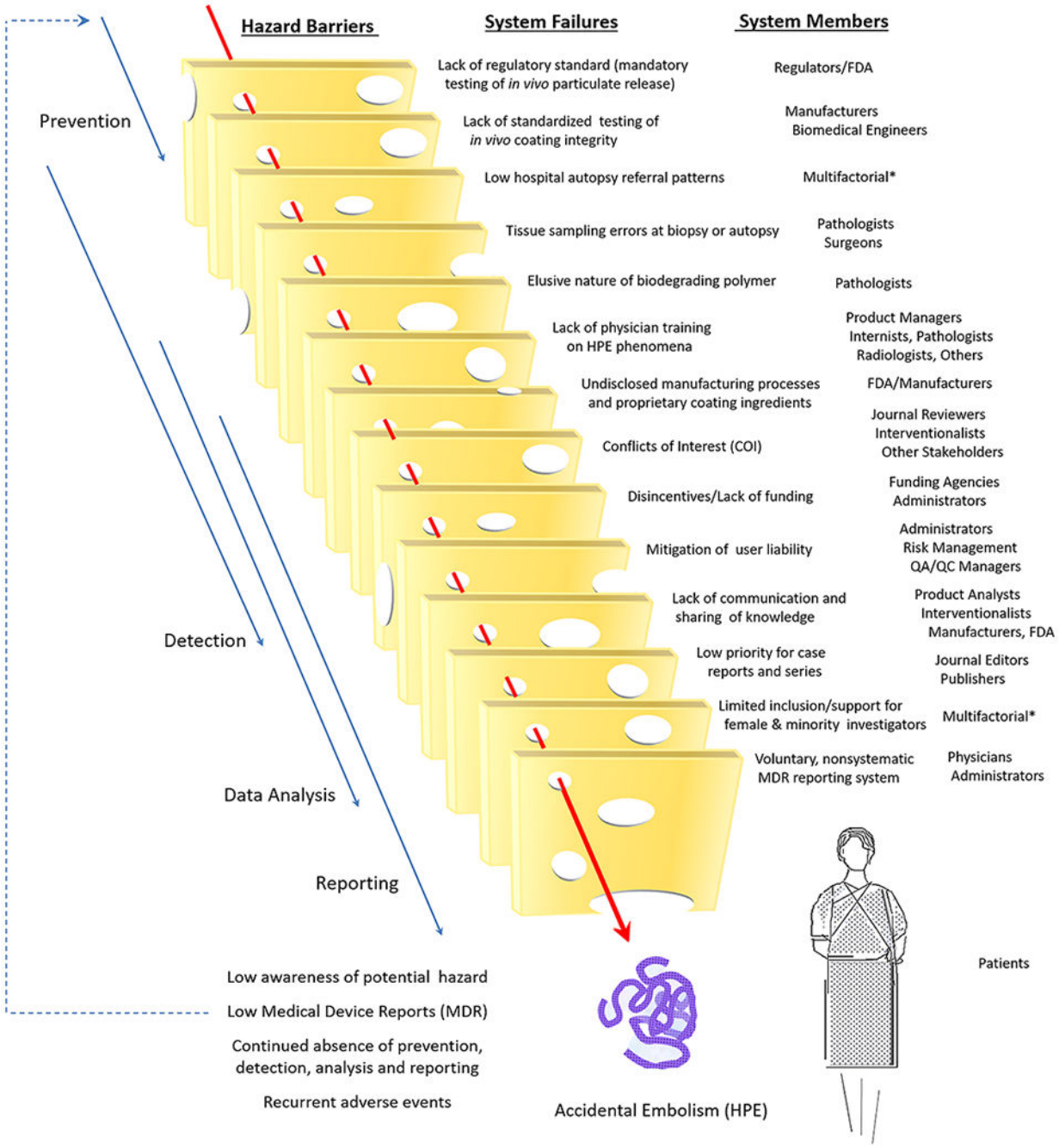

Figure 3. Postmarket HPE Surveillance: Current Hazard Barriers, System Members and System Failures

Historically, medical device reports (MDRs) have been used for primary device surveillance. MDRs submitted through MedWatch are entered into the Manufacturer and User Facility Device Event (MAUDE) database and are monitored by the Office of Suveillance and Biometrics (OSB) to identify device problems and determine trends. Abbreviations: FDA, Food and Drug Administration; QA, quality assurance; QC quality control. *Multifactorial, beyond the scope of the current manuscript

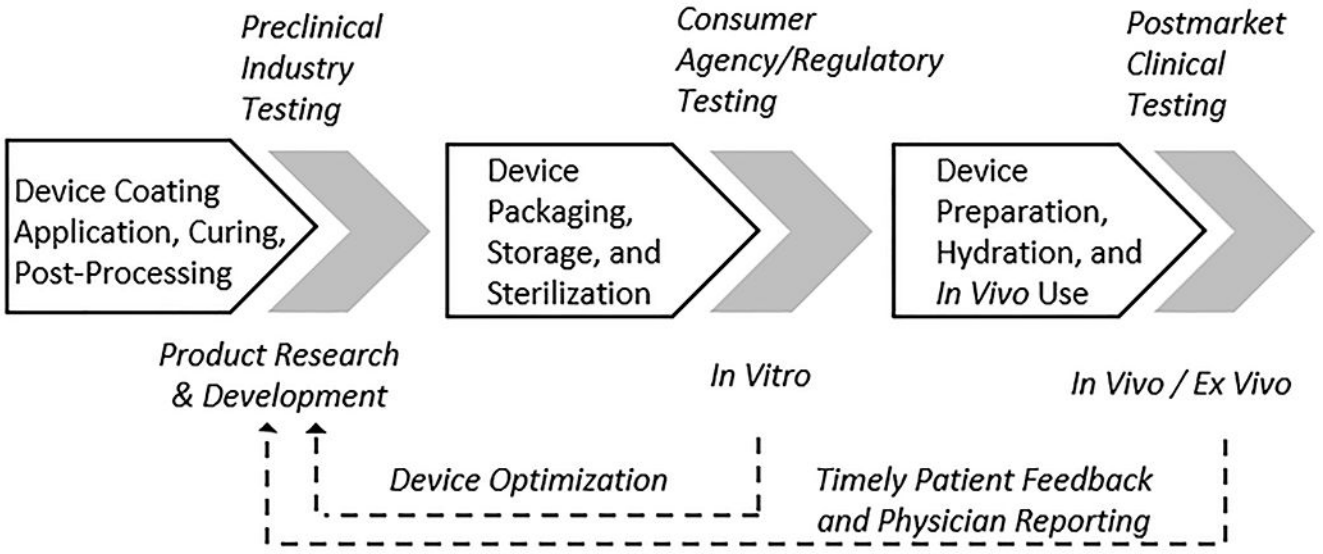

Figure 4. Proposed Changes for Device Particulate Evaluation and Testing

Ideally, testing for coating particulates and device safety should occur at different stages of product lifecycles, during manufacturing, approval, and postmarket use, to assess for quality and risks of coating delamination in variable real-world settings.

Table 1

Documented HPE Cases: Published Clinical Reports and Author Consult Data, with Patient Numbers.

Year	Authors	Tissue or Organ(s) Affected (Number of Patients)	Access Site vs. Distal Embolic Event	Reference
1997	Barnwell SL *et al.*[2]	Brain (4)	Distal	2
2003	Kozak M *et al.*[13]	Skin (10)	Access Site	13
2003	Subramanian R *et al.*[12]	Skin (1)	Access Site	12
2005	Ziakas A *et al.*[14]	Skin (1)	Access Site	14
2008	Fealey ME *et al.*[3]	Brain (1) Skin (2)	Access Site Distal	3
2009	Mehta RI *et al.*[8]	Brain (1)	Distal	8
2009	Allen RW *et al.*[4]	Lung (1)	Distal	4
2010	Mehta RI *et al.*[9]	Brain (2) Lung (5) Skin (1)	Distal	9
2012	El-Najjar V *et al.*[19]	Heart (1)	Distal	19
2012	Schipper ME *et al.*[20]	Heart (1)	Distal	20
2013	Sequeira A *et al.*[21]	Heart (1) Kidney (1) Arteriovenous graft (1)	Distal	21
2014	Hu YC *et al.*[22]	Brain (3)	Distal	22
2014	Sanon S *et al.*[24]	Heart (1)	Distal	24
2014	Rosen LE *et al.*[27]	Heart (1)	Distal	27
2014	Danowski KM *et al.*[25]	Skin (1)	Distal	25
2014	Hamidi S *et al.*[26]	Skin (1)	Distal	26
2015	Mehta RI *et al.*[5]	Lung (18) Brain (1) Heart (1)	Distal	5
2015	Hardy CL *et al.*[32]	Skin (1)	Distal	32
2015	Chen CL *et al.*[23]	Kidney (1)	Distal	23
2015	Thompson AK *et al.*[31]	Skin (8)	Distal	31

Year	Authors	Tissue or Organ(s) Affected (Number of Patients)	Access Site vs. Distal Embolic Event	Reference
2015	Shapiro M *et al.*[30]	Brain (2)	Distal	30
2015	Fujisaka T *et al.*[29]	Heart (1)	Distal	29
2015	Grundeken MK *et al.*[33]	Heart (4)	Distal	33
2016	Mehta RI *et al.*[15]	Brain (6)	Distal	40
2016	Goto K *et al.*[37]	Skin (1)	Distal	37
2016	Chavez JA *et al.*[35]	Colon (2) Aorta (1)	Distal	35
2016	Lorentzen AO *et al.*[38]	Brain (1)	Distal	38
2016	Rapkiewicz A *et al.*[28]	Lung (1)	Distal	28
2010-2016	Mehta (unpublished)	Lung (39) Liver (7) Brain (15) Heart (9) Colon (8) Spleen (4) Muscle (2) Kidney (4) Pancreas (2) Adrenal Gland (1) Arteriovenous graft (1) Skin (1)	Distal	N/A

Table 2

Documented HPE Particulate Sizes, Organ-Specific Effects and Adverse Reaction Patterns.

Organ	Maximum Particulate Size, C.S.*	Maximum Particulate Size, L.*	Potential Acute Events	Potential Subacute or Delayed Events
Lungs	1.9 mm	2.3 cm	Acute pulmonary embolism Death	Pulmonary infarction Pulmonary granulomas Pulmonary vasculitis Pulmonary thrombosis Pulmonary abscesses Pulmonary/mediastinal lymphadenopathy Death
Brain, Intracerebral Tissue or Spinal Cord	590 μm	1.5 cm	Focal neurological deficits Coma/mental status change Meningismus/headache Hemorrhagic stroke Ischemic stroke Death	Focal neurological deficits Meningismus/headache Coma/mental status change Cerebral vasculitis Cerebral granulomas Cerebral abscesses Cerebral thrombosis Cerebral white matter loss Seizure/involuntary movements Secondary hydrocephalus Hemorrhagic stroke Anoxic brain injury Death
Heart	530 μm		Arrhythmia Cardiac thrombosis Myocardial hemorrhage Myocardial infarction Death	Arrhythmia Cardiac thrombosis Cardiac granulomas Myocardial hemorrhage Cardiac vasculitis Myocardial infarction Death
Kidney	520 μm	1.0 cm	Acute renal failure	Oliguric renal failure Renal abscesses Hematuria
Liver	510 μm		Acute hepatic hemorrhage	Hepatic vasculitis Hepatic granulomas Hepatic infarction Hepatic abscesses
Colon	400 μm		Acute gastrointestinal hemorrhage	Ischemic colitis

Organ	Maximum Particulate Size, C.S.*	Maximum Particulate Size, L.*	Potential Acute Events	Potential Subacute or Delayed Events
				Colonic granulomas Colonic vasculitis Colonic abscesses Delayed gastrointestinal hemorrhage Retroperitoneal lymphadenopathy
Arteriovenous Graft	340 μm		Acute graft hemorrhage	Chronic graft arteritis Graft thrombosis Delayed graft hemorrhage
Skin/Extremities	500 μm	8.8 mm	Purpura, dermal hemorrhage	Purpura, dermal hemorrhage Induration/ulceration Deep vein thrombosis Livedo reticularis Ecchymoses Panniculitis Gangrene
Pancreas	200 μm		Acute pancreatic hemorrhage	Pancreatic granulomas Patchy pancreatic necrosis Scattered chronic pancreatitis Pancreatic abscesses
Spleen	200 μm		Subcapsular hemorrhage	Splenic granulomas
Muscle	180 μm		Intramuscular hemorrhage	Muscle granulomata Patchy myositis
Adrenal Gland	100 μm		Adrenal cortical hemorrhage	Focal adrenal microhemorrhage
Systemic Effects	Variable	Variable	Multifocal hemorrhage Constitutional Symptoms (Fever, Chills, Malaise, Syncope), Death	Multifocal vasculitis Constitutional Symptoms Systemic lymphadenopathy Multiple organ failure Multifocal embolic infarcts Multifocal thrombosis and hemorrhage Disseminated intravascular coagulation Systemic inflammatory response syndrome Death

* Indicates greatest detected cross-sectional (C.S.) or longitudinal (L.) HPE dimension, where identifiable or reported. Findings were confirmed on diagnostic light microscopy and/or extrapolated by a pathologist based on submitted light microscopic data.

Table 3

Primary System Failures and Potential Improvements for Enhanced Device Quality and Safety

Primary System Failures	Potential Quality and System Improvements
Lack of Defined Regulatory Standards	**Update Regulatory Standards and Safety Requirements for Coated Vascular Devices**
➢Absence of systematic *in vivo* particulate testing (i.e., animal model and/or clinical evaluation)	➢Conduct systematic, prospective device-specific testing for *in vivo* particulate release, to assess coating integrity and end-organ effects in animal models and/or patient subsets
Disincentives and Lack of Incentives for Investigating and Reporting on Device Events	**Strengthen Postmarket Surveillance Initiatives**
➢Lack of support, resources, time and funding for research and postmarket surveillance initiatives	➢Reimburse for select medical autopsies and quality and safety improvement initiatives; allocate funding and institutional support for research and event reporting
➢Liability issues for hospitals and treating physicians	**Support Individual Physicians and Investigators**
Lack of Communication/Miscommunications Among Physicians and System Members	➢Flag potential hazards for expanded investigation
➢Lack of transparency and feedback	➢Encourage investigation of novel hypotheses
Over-Reliance on Medical Device Reports (MDRs) as a Primary Postmarket Surveillance Tool	**Foster Team-Based Investigational Approaches**
➢Limitations on utility and timeliness of passive device reporting and nonintegrated surveillance methods	➢Encourage joint prospective initiatives between diagnostic physicians-treating physicians-regulators-manufacturers
Conflicts of Interest Among Stakeholders	➢Pool multi-institutional post-procedural outcome data
➢Inherent biases of manufacturers and device users	➢Create regional and national clinical databases
Resistance to Challenging Established Guidelines	➢Create centralized tissue and device registries
➢Impediments in declaring unexpected new findings	**Mitigate Biases and Conflicts of Interest**
Delays in Disseminating Postmarket Findings	➢Advocate for non-biased investigation and reporting
➢Publication delays and gaps in physician alerting	**Facilitate Public Availability of Postmarket Data**
	➢Disclose cytotoxicity/immunotoxicity and particulate release data regarding individual proprietary coatings and devices